REMARKS

Reconsideration and reexamination of the subject application, as amended, in light of the remarks which follow, pursuant to and consistent with 37 C.F.R. § 1.112, are respectfully requested.

Turning now to the Office Action, Applicants acknowledge the objection to the oath. The undersigned respectfully advises that a substitute oath or declaration will be submitted upon indication that this application is otherwise in condition for allowance.

Claims 14 and 15 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification to enable one skilled in the art to which it pertains or with which it is most nearly connected, to make and/or use the invention. This rejection is respectfully but strenuously traversed.

In particular, the Examiner alleges that the recitation "non-radiolabelled" in claim 11 does not find support in the as-filed disclosure. More specifically, this claim is directed to administration of a non-radiolabeled chimeric anti-CD20 antibody in combination with at least one chemotherapeutic agent. Applicants respectfully maintain that this limitation finds support in the section of the disclosure which the undersigned previously referred the Examiner to in previous Reply. Specifically, this limitation finds support at page 61 of the application, wherein treatment with a chimeric anti-CD20 antibody which is non-radiolabeled, i.e., C2B8, is combination

with at least one chemotherapeutic agent is described. Specifically, the Examiner is respectfully referred to page 61, lines 22-23, and the lines which follow this section of the disclosure. Moreover, it would be readily apparent, since the application refers to radiolabeled antibodies differently than C2B8, on this same page, that referral to C2B8, means necessarily that this antibody is not attached to a radiolabel. For example, the Examiner is respectfully referred to page 61, line 6, wherein Applicants refer to radiolabeled 2B8 and radiolabeled Y2B8. It should be noted that Applicants do not refer to these radiolabeled antibodies as 2B8 or Y2B8. Rather, Applicants are careful to distinguish a radiolabeled antibody from a non-radiolabeled antibody. Therefore, it is respectfully maintained that the phraseology in the disclosure finds at least implicit support at this section of the application. Moreover, if the Examiner elects to maintain this rejection, which Applicants respectfully submit is without basis, he is respectfully requested to suggest alternative phraseology since it would be absolutely clear from the as-filed disclosure that the claims are adequately supported by the teachings of the as-filed application. Based on the foregoing, withdrawal of this basis of the § 112, first paragraph, rejection of claims 11-15 is respectfully requested.

Also, the Examiner alleges that the specification does not describe in the parent application a method which utilizes a mixture of different chemotherapeutic agents in combination with C2B8. However, the position of the Examiner is respectfully

believed to be in error. To the contrary, the parent application refers to CHOP chemotherapy, which utilizes a combination of four different chemotherapeutic agents. Moreover, such chemotherapeutic regimen is disclosed in conjunction with C2B8 administration. Therefore, contrary to the Office Action, this claimed limitation also finds clear support in the parent application. In particular, the Examiner is respectfully referred to column 32, wherein Applicants describe preferred chemotherapeutic agents and specifically incorporate by reference Armatage, J.O. et al, *Cancer*, 50:1695 (1982), which describes the CHOP therapeutic regimen. Therefore, based on the foregoing, withdrawal of the § 112, first paragraph, rejection of claims 11-15 is respectfully requested.

Claims 11-15 further stand rejected under 35 U.S.C. § 102(e) as allegedly being anticipated by Anderson et al (U.S. Patent No. 5,736,137). This rejection is made, because of the different inventive entity, namely the fact that John Leonard was removed as an inventor of the parent application. The Examiner is respectfully advised that John Leonard is also not an inventor of this application. A declaration to remove John Leonard as an inventor will be submitted in order to obviate this issue. Therefore, the Examiner is respectfully requested to hold this rejection is abeyance until submission of this declaration. Essentially, this declaration will state, as in the parent application, that John Leonard's contribution relates to the use of a radiolabeled anti-CD20 antibody, which is not the subject of any claim of this application.

Claim 11 stands rejected under 35 U.S.C. § 102(e) as anticipated by or, in the alternative, under 35 U.S.C. § 103(a) as obvious over Kaminski et al (U.S. Patent No. 5,595,721). This rejection is also respectfully traversed.

Essentially, the position of the Examiner is that Kaminski teaches the use of a chimeric anti-CD20 antibody, which would render obvious use of a chimeric andi-CD20 antibody according to the present invention, based on their prophetic disclosure relating to an antibody which causes apoptosis of cells which are bound by said antibody. The Examiner refers in particular to column 7 and column 33 of the Kaminski patent. Also, the Examiner maintains the rejection on the basis that "the Patent Office does not have the facilities for examining and comparing the method of the instant invention to those of the prior art, [therefore] the burden is on applicant to show an unobvious distinction between the method of the instant invention and that of the prior art."

This rejection is respectfully traversed for substantially the same reasons set forth in Applicants' previous reply. Essentially, Applicants are claiming the use of a chimeric anti-CD20 antibody which possesses non-obvious biological characteristics *vis-à-vis* conventional chimeric anti-CD20 antibodies. This was convincingly demonstrated based on a declaration submitted during prosecution of the parent application, i.e., U.S. Serial No. 08/149,099, a copy of which was submitted with Applicants' previous reply. Moreover, this declaration was found persuasive to

overcome prior art rejections, which had been made in the parent application. Essentially, the Applicant demonstrated the non-obvious characteristics, i.e., the substantial B cell depleting activity of chimeric anti-CD20 antibodies according to the invention. Therefore, Applicants respectfully submits that the § 103 rejection is inconsistent with the Examiner's previous determination of patentability.

Also, the Examiner's statement with respect to the Patent Office's inability to make a comparison, is curious, because the Kaminski patent does not exemplify any chimeric anti-CD20 antibody. To the contrary, the patent only contains a prophetic disclosure relating to a chimeric anti-CD20 antibody. Therefore, it is unclear as to what comparison the Examiner would like Applicants to make.

In fact, Applicants respectfully submits that they have already provided a convincing comparison, which should have been sufficient to overcome this rejection. Again, in the previously submitted § 132 declaration, they provided comparative data substantiating that chimeric anti-CD20 antibodies of the present invention possess enhanced properties *vis-à-vis* other chimeric anti-CD20 antibodies. There is no reasonable basis for asserting that an additional comparison should be provided, especially given the fact that Kaminski does not even exemplify a chimeric anti-CD20 antibody in their disclosure. Essentially, in order to make the Examiner's apparent suggested comparison, Applicants would have to construct a chimeric anti-CD20 antibody, using the murine anti-CD20 antibody described by Kaminski. However,

Applicants respectfully submits that this is an unreasonable burden on Applicants, especially given the fact that they have already provided a convincing demonstration of unexpected results which convinced the Examiner previously to allow claims directed to a particular antibody possessing the B cell depleting activity recited in claims 11-15. Therefore, based on the foregoing, withdrawal of the § 103 rejection of claim 11 based on Kaminski et al is respectfully requested.

Claims 11-13 also stand rejected under 35 U.S.C. § 103(a) as assertedly being unpatentable over the combination of Press et al (*Blood*) in view of Hellstrom et al (WO 92/07466) and Robinson et al (U.S. Patent No. 5,500,362).

Essentially, the position of the Examiner is that Press et al disclose the use of a murine anti-CD20 antibody for the treatment of B cell lymphoma, that Hellstrom discloses the advantages of chimeric antibodies for therapeutic treatment based on their increased immune function, and based on the fact that they contain human efficacy regions, and that Robinson teaches the use of a chimeric anti-CD20 antibody to treat B cell lymphoma and the advantages of such antibodies. Based thereon, the Examiner concludes that the claimed methods would have been obvious.

However, again, Applicants respectfully submits that the § 103 rejection, is inconsistent with the Examiner's previous determination of patentability in the parent application.

Turning to the specific references, Press et al certainly does not teach or suggest the claimed invention, because it is directed to use of a murine chimeric anti-CD20 antibody. Moreover, even when this reference is combined with Hellstrom et al and Robinson et al, the combination does not teach or suggest the claimed invention. It is agreed that there existed prior art suggesting the use of chimeric anti-CD20 antibodies as potential therapeutics. However, contrary to the Office Action, Robinson et al would not have fairly suggested a chimeric antibody possessing the B cell depleting activity of the present invention. Nor would this be obvious based on Press et al.

In fact, the unexpected result obtained by the present invention, i.e., the fact that chimeric anti-CD20 antibodies could be obtained having the recited B cell depleting activity, could not have been reasonably predicted at the time of the invention. This fact, again, is supported by the previously submitted declaration by Dr. Anderson, an inventor of the subject application. Therein, Dr. Anderson compared the B cell depleting activity of chimeric antibody according to the present invention to other chimeric anti-CD20 antibodies. Again, it may be seen that the comparative anti-CD20 antibodies did not possess the B cell depleting activity within the range of claims 11-15. Moreover, in order to expedite prosecution, claim 11 has been amended to recite that the administered dosage of the chimeric antibody is about 0.4 mg/kg body weight. As 0.4 is the initial part of the described dosage regimen, for

example at page 15, line 9, and page 16, line 12, the Examiner cannot assert that this dosage regimen does not find support in the as-filed disclosure.

Moreover, such limitation of the claims clearly should obviate the rejection made based on Press et al. Indeed, as argued in Applicants' previous reply, the antibody disclosed by Press et al, i.e., IF5, only exhibits depleting activity at very high dosages, i.e., at dosages in excess of greater than 2 grams. Moreover, even these results are transient. Therefore, the murine anti-CD20 antibody of Press et al does not possess the properties of the chimeric anti-CD20 antibodies recited in the claimed methods. Similarly, the secondary references do not support a conclusion that antibodies possessing such properties would have been obvious, based on the previously submitted § 132 declaration. Therefore, withdrawal of the § 103 rejection of claims 11-13 based on Press et al in view of Hellstrom et al and Robinson et al is respectfully requested.

Finally, claims 11-15 stand rejected under 35 U.S.C. § 103(a) as assertedly being unpatentable over Hellstrom et al in view of Robinson et al, Reff et al (*J. Cell. Biochem.*) or Reff et al (*Blood*) or Anderson et al.

Again, the Examiner has cited a plurality of references to support his position that the claimed therapeutic methods would have been obvious because the use of murine and chimeric anti-CD20 antibodies as potential therapeutics had been

previously described. Specifically, this is supported by the five above-identified references.

At the outset, it is noted that all of these references were cited during the parent application, and Applicants overcome a § 103 rejection based thereon, in view of the enhanced properties of chimeric anti-CD20 antibodies according to the invention. Essentially, Applicants respectfully maintain that it could not have been reasonably predicted prior to the present invention that a chimeric anti-CD20 antibody, possessing the B cell depleting activity of the antibodies according to the invention could have been obtained absent undue experimentation. This position is convincingly established by the § 132 declaration by Dr. Anderson, which was submitted during prosecution of the parent application, a copy of which is of record in this application.

Applicants respectfully maintain that the Examiner has provided no convincing reasoning, which would reasonably suggest that antibodies possessing the recited B cell depleting activity would have been obvious based on these references.

Therefore, based on the foregoing, withdrawal of the § 103 rejection of claims 11-15 based on Hellstrom in view of Robinson et al, Reff et al (both references) and Anderson et al is respectfully requested.

Based on the foregoing, this application is believed to be in condition for allowance. A Notice to that effect is respectfully solicited. However, if any issues

remain outstanding after consideration of this reply, the Examiner is respectfully requested to contact the undersigned so that prosecution may be expedited.

Respectfully submitted,

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